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<p>(21) International Application Number: PCT/US96/10160 (22) International Filing Date: 12 June 1996 (12.06.96) (30) Priority Data: 08/489,352 12 June 1995 (12.06.95) US (60) Parent Application or Grant (63) Related by Continuation US 08/489,352 (CIP) Filed on 12 June 1995 (12.06.95) (71) Applicant (for all designated States except US): THERMO- LASE CORPORATION [US/US]; 10455 Pacific Center Court, San Diego, CA 92121-4339 (US). (72) Inventor; and (75) Inventor/Applicant (for US only): TANKOVICH, Nikolai I. [RU/US]; 2361 Stargate Avenue, San Diego, CA 92129 (US). (74) Agent: FRENCH, Timothy A.; Fish &amp; Richardson P.C., 225 Franklin Street, Boston, MA 02110 (US).</p>		<p>(81) Designated States: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).</p> <p>Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i></p>
<p>(54) Title: LASER ASSISTED DRUG DELIVERY</p> <div data-bbox="324 1155 1299 1491"></div> <p>(57) Abstract</p> <p>The present invention provides a process for laser assisted drug delivery through the skin. A drug (4) and an explosive absorber (2) of light energy are applied topically to the skin. The treated area of the skin is illuminated with very short pulses of light which are preferentially absorbed by the absorber causing a very large number of tiny explosions. The explosions force portions of the drug to penetrate into the skin. A preferred embodiment utilizes small graphite particles and an Nd:YAG short pulse laser.</p>		

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### **LASER ASSISTED DRUG DELIVERY**

This invention is a continuation in part of Serial No. 08/489,352 filed 6/12/95 which was a continuation in part of Serial No. 08/280928 filed 7/26/94, Serial No. 08/257,021 now U.S. Patent No. 5,423,803 on 6/13/95, and  
5 Serial No. 08/005,810 filed 1/19/93, now U.S. Patent No. 5,425,728 on 6/20/95 which was a continuation in part of Serial No. 07/783,789 filed 10/29/91, now Patent No. 5,226,907 issued July 13, 1993. This invention relates to processes and equipment for drug delivery skin treatment and in particular equipment and procedures for delivering drugs through skin to such processes which  
10 utilize lasers.

### **BACKGROUND OF THE INVENTION**

A section of human skin showing a cross section of one hair is shown in FIG. 1. FIG. 1 shows the hair shaft 33 of a hair growing in a hair duct 31, from dermal papilla 32, a nerve ending 34, a sweat gland 35 a  
15 sebaceous gland 38, arteries 36 and veins 37.

The epidermis, 39 in FIG. 1, of the human skin comprises several distinct layers of skin tissue. The deepest layer is the stratum basale layer which consists of columnar cells. The next layer up is the stratum spinosum composed of polyhedral cells. Cells pushed up from the stratum spinosum are  
20 flattened and synthesize keratohyalin granules to form the stratum granulosum layer. As these cells move outward they lose their nuclei and the keratohyalin granules fuse and mingle with tonofibrils. This forms a clear layer called the stratum lucidum. The cells of the stratum lucidum are closely packed. As the cells move up from the stratum lucidum they become compressed into many  
25 layers of opaque squamas. These flattened cells have become completely filled with keratin and have lost all other internal structure, including nuclei. These squamas constitute the outer layer of the epidermis, the stratum corneum. At the bottom of the stratum corneum the cells are closely compacted and adhere to one another strongly, but higher in the stratum they  
30 become loosely packed and eventually flake away at the surface.

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There exists many prior art methods for drug delivery through the skin. These include injection with a hypodermic needle, high pressure injectors, electrophoresis techniques, sonophoresis techniques and dermo patches. A laser assisted method of drug delivery has recently been proposed  
5 in which a laser is used to evaporate tiny holes in an area of the skin afterwhich a drug is applied to the treated area. It is known that infiltration of drugs through the skin can be increased by forcing the drug into hair follicles.

It is known that graphite vaporizes at about 3,600°C. It is known that graphite is a strong absorber of infrared light and that infrared light such  
10 as the 1.06 micron laser beam produced by the Nd:YAG laser will penetrate several millimeters through human skin.

What is needed is a simple quick treatment process for drug delivery through the skin.

#### SUMMARY OF THE INVENTION

15 The present invention provides a process for laser assisted drug delivery through the skin. A drug and an explosive absorber of light energy are applied topically to the skin. The treated area of the skin is illuminated with very short pulses of light which is preferentially absorbed by the absorber causing a very large number of tiny explosions. The tiny explosion forces  
20 portions of the drug to penetrate into the skin. A preferred embodiment utilizes small graphite particles and an Nd:YAG short pulse laser. Another preferred embodiment utilizes a mixture of potassium nitrate, carbon powder and sulfur (normally known as black powder) with the Nd:YAG laser.

#### BRIEF DESCRIPTION OF THE DRAWINGS

25 FIG. 1 shows a skin section.

FIGS. 2-5 and Figs. 6A and 6B are drawings demonstrating four embodiments of the present invention.

FIG. 7 shows a skin surface.

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**DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS**

Applicant has discovered that when small particles of graphite are illuminated with very short pulses of laser light of sufficient energy the individual particles explode violently. If the pulse-duration and energy is  
5 chosen correctly carbon particles in the 1 micron size range will violently break apart into smaller fragments. Subsequent pulses continue to break the particles into even smaller sizes until the particles disappear. For example, in an inert atmosphere after repeated illumination with 1.06 micron, 12 nanosecond, 3 Joules per  $\text{cm}^2$  pulses, the particles are broken into extremely  
10 small particles barely visible to the unaided eye. But in air the particles after such repeated illumination disappear completely, apparently forming  $\text{CO}_2$ .

A preferred embodiment of the present invention utilizes the explosive force created by the partial or complete vaporization of small particles in very short time intervals in order to force drugs into the body  
15 through skin tissue.

**FIRST EMBODIMENT****Carbon particles - Nd:YAG Laser - Drug**

Our basic preferred process can be explained as follows. We utilize an Nd:YAG laser producing 12 nanosecond laser pulses at 1.06 microns with  
20 an energy per pulse of about 1.5 Joule and a laser cross section of about  $0.5 \text{ cm}^2$  to produce a beam of about 3 Joules per  $\text{cm}^2$ . A mixture of the drug to be delivered and small graphite particles is prepared. We prefer particles having dimensions of about 1 micron. The mixture is applied topically to the skin and rubbed into it so that portions of the mixture is infiltrated into spaces  
25 in the skin. These spaces include small cracks in the epidermis and hair follicles. The treated section of the skin is then illuminated with the pulse beams described above. FIG. 7 is a drawing showing the graphite particles 2, the drug 4 and epidermal cells 3.

Graphite is very absorptive of laser energy at the  $1.06 \mu\text{m}$   
30 wavelength. The latent heat of vaporization is about  $10^5 \text{ J/cm}^3$  for cold solid

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graphite. (The energy required to heat room temperature graphite to the sublimation temperature is roughly 4% of the sublimation energy.) Thus, to vaporize a 1 micron cube ( $10^{-12}$  cm<sup>3</sup>) would require approximately  $10^{-7}$  J. The energy falling on the surface of the 1 micron particle ( $1 \times 10^{-8}$  cm<sup>2</sup>) in a 5 3J/cm<sup>2</sup> pulse is  $3 \times 10^{-8}$  J, about one third of the energy needed to totally vaporize the particle. Therefore, a significant portion of the particle is vaporized. The energy is deposited in a few nanoseconds so there is no time for the heat to diffuse; therefore, the particle explodes violently upon being illuminated by the pulse. (Subsequent pulses will vaporize the smaller particles 10 created by the earlier pulses.) The resulting forces of the tiny explosions force a portion of the drug into the skin tissue where it is absorbed into the body.

#### Drug List

The following are drugs which could be applied using the process described above.

15        Drugs (in the form of ointment and liquid solution or emulsion) to be delivered trans cutaneously by the laser forcing method:

- Antibiotics: Bacitracin-Neomycin-Polyxin B
- Antibacterial: Mycostatin
- Hormones: Hydrocortisone
- 20        • Vasodilators: Minoxidil
- Chemotherapeutic Drugs: Adriamycin
- Anesthetics: Lidocaine
- Immunomodulators: Intron A
- PDT Sensitizers: ALA, HPD, Photophrin
- 25        • Anticoagulants: Heparin
- Nitrites: Nitroglycerin
- Enzymes: Streptase
- Deposition Forms: Liposomes, Magnetic Fluid Drugs,
- Coacervates
- 30        • Radio Isotops: Be, Cd

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In all cases our preferred treatment is to mix these drugs directly with one micron graphite particles at a weight ratio of about 20% carbon to 80% drug.

### ENHANCEMENTS

5           The following are techniques for enhancing the effects of the above process.

One method of enhancement is to infiltrate the graphite drug mixture into hair follicles prior to illumination as shown in FIG. 5. The graphite particles are 2 and the drug 4. The walls of the follicles are much  
10 thinner than the epidermis so entry in the dermis portion of the skin is greatly enhanced upon illumination.

FIG. 3 shows the drug applied first and carbon particles applied on top of the drug. A transparent tape can be applied over the graphite drug mixture shown in FIG. 3 prior to illumination as shown in FIG. 6A.

15 Illumination results in explosive forces as depicted in FIG. 6B.

A glass cover such as a microscope slide can be applied with about 1 psi pressure during illumination to enhance shock waves caused by the drug explosions. The glass could be a part of an articulated arm delivering the laser beam.

### 20           OTHER EMBODIMENTS

Persons skilled in the laser medicine art will recognize that there are a great many ways to practice this invention other than the few described above. Many particles in addition to graphite will explode upon illumination with short laser pulses. Particles chosen, however, must have a high absorption  
25 at the wavelength of the laser chosen. There are many short pulse lasers other than the Nd:YAG laser which could be utilized. Explosive chemicals such as black powder which explodes upon illumination with laser pulses can be used. Black powder is a mixture of potassium nitrate ( $\text{KNO}_3$ ) carbon powder and sulfur. One such mixture is 75%  $\text{KNO}_3$ , 15% carbon and 15% sulfur. The  
30 constituents are very finely ground. Again a match with the particles must be

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assured. As an alternate to mixing the particles and the drug as shown in Fig. 2; the drug could first be applied to the skin in a layer and a second layer of graphite particles could be applied over the drug layer as shown in FIG. 3. The particles could be coated individually with a drug as shown in FIG. 4.

5           Thus, the reader should not construe the above examples as limitations on the scope of the invention, by merely as exemplifications of preferred embodiments thereof. Those skilled in the art will envision many other possible variations are within its scope. Accordingly the reader is requested to determine the scope of the invention by the appended claims and  
10 their legal equivalents, and not by the examples which have been given.



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We claim:

1. A process for transdermal drug delivery comprising the steps of:
  - a. topically applying to a section of skin a drug and an explosive  
5 absorber, said absorber having a high absorption at at least one frequency band of light,
  - b. illuminating said section of skin with pulses of said at least one frequency band of light, so as to impart to the absorber sufficient energy to cause at least a portion of said to explode with the resulting explosion  
10 forcing at least a portion of said drug into said skin.
2. A process as in Claim 1 wherein said absorber comprises a large number of carbon particles.
3. A process as in Claim 1 wherein a confinement means,  
transparent to said at least one frequency band of light is placed firmly over  
15 said topically applied drug and absorber for the duration of said forcing explosion for the purpose of confining said forcing explosion.
4. A process as in Claim 5 wherein said confinement means is a glass plate.
5. A process as in Claim 5 wherein said confinement means is a  
20 plastic plate.
6. A process as in Claim 7 wherein said plastic plates is a part of an articulated arm.
7. A process as in Claim 2 wherein said small carbon particles are small graphite particles.
- 25 8. A process as in Claim 2 wherein said small carbon particles have major dimension of about 1 micron.
9. A process as in Claim 2 wherein said laser pulses are pulses from a Nd:YAG laser.

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10. A process as in Claim 2 wherein said laser pulses are pulses from a CO<sub>2</sub> laser.

11. A process as in Claim 1 and further comprising the additional step of forcing said drug and absorber into spaces in said skin section prior to  
5 illumination.

12. A process as in Claim 11 wherein said spaces comprise hair ducts.

13. A process as in Claim 11 wherein said spaces in said skin comprises spaces between superficial epidermal skin cells.

10 14. A process as in Claim 11 wherein said spaces in said skin comprises spaces within sebaceous glands.

15. A process as in Claim 2 wherein said spaces in said skin comprise spaces adjacent to sebaceous glands.

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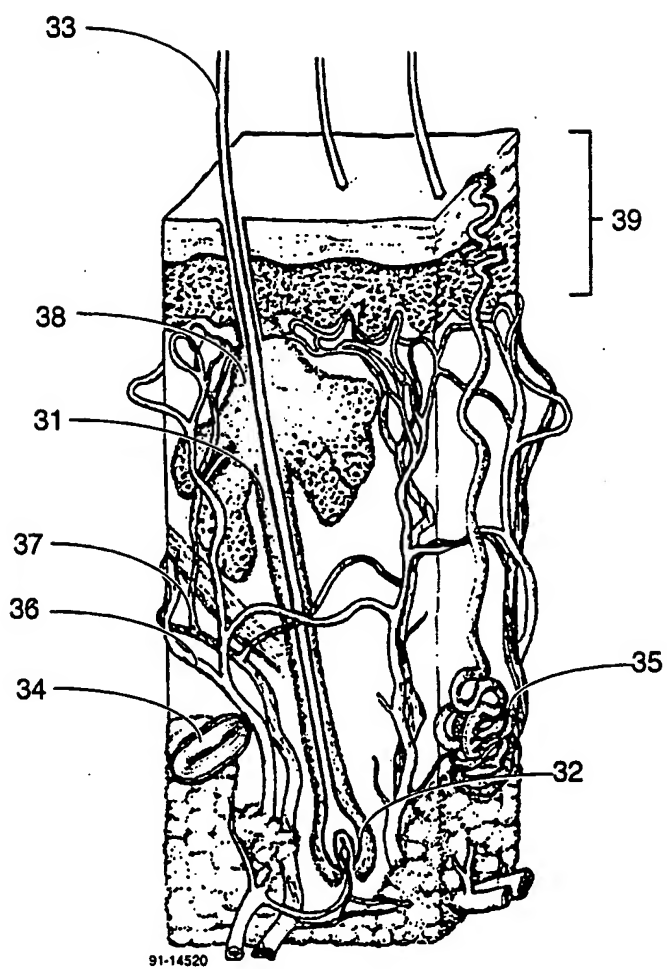


FIG. 1

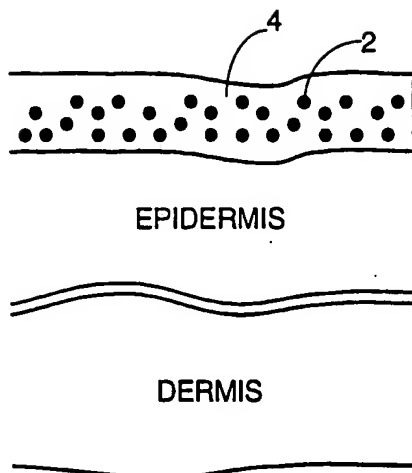


FIG. 2

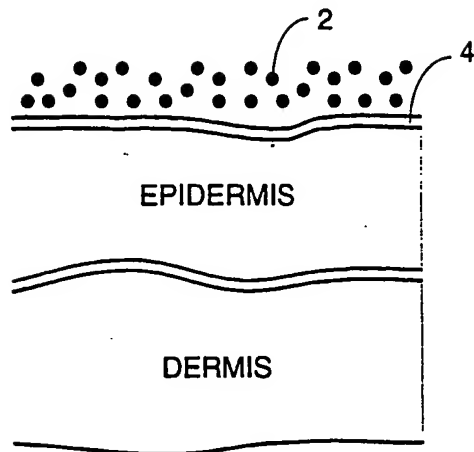
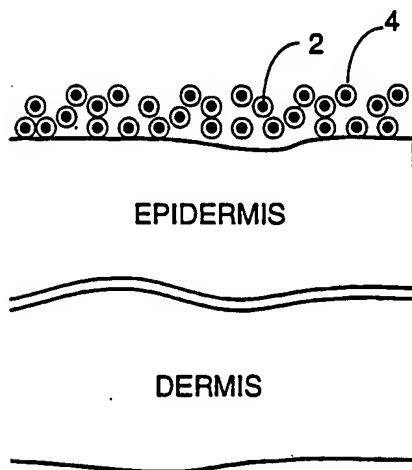


FIG. 3



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FIG. 4

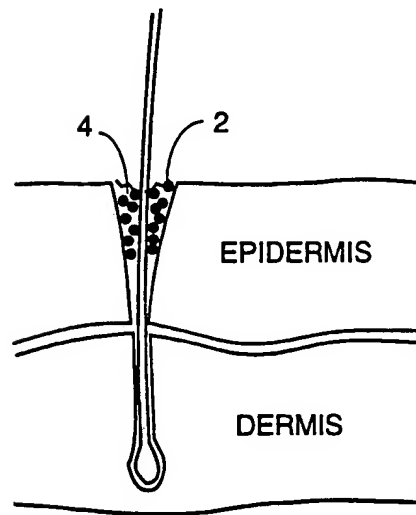


FIG. 5

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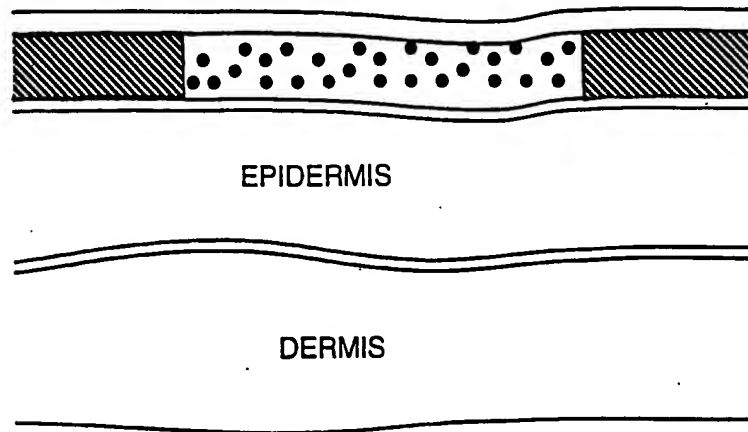


FIG. 6A

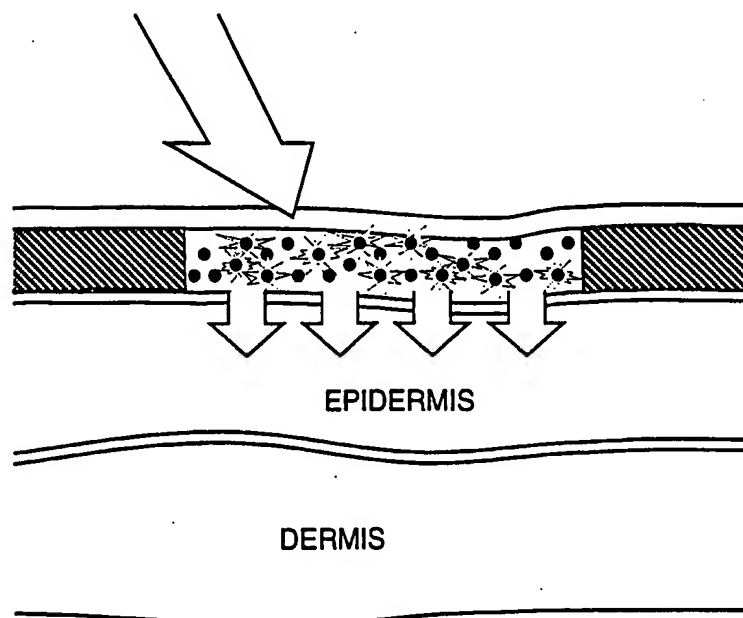


FIG. 6B

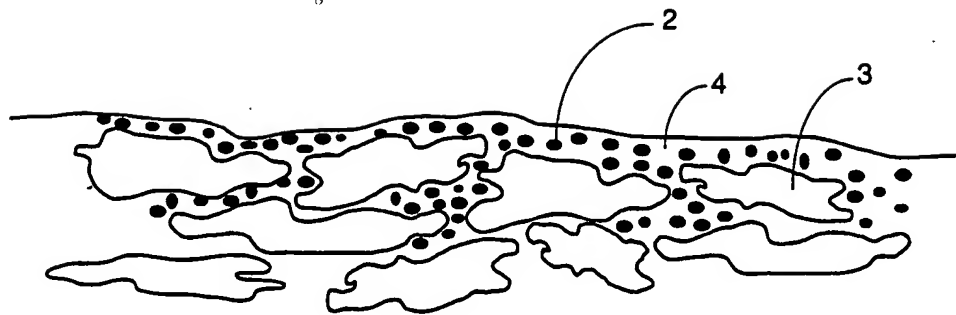


FIG. 7

## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US96/10160

<b>A. CLASSIFICATION OF SUBJECT MATTER</b>		
IPC(6) :A61N 05/06 US CL :606/9 According to International Patent Classification (IPC) or to both national classification and IPC		
<b>B. FIELDS SEARCHED</b>		
Minimum documentation searched (classification system followed by classification symbols) U.S. : 128/898; 601/2; 604/20, 22, 49, 290; 606/1-9, 131, 133; 607/88-90		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)		
<b>C. DOCUMENTS CONSIDERED TO BE RELEVANT</b>		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	US 5,423,803 A (TANKOVICH et al) 13 June 1995, entire document.	1-15
<input type="checkbox"/> Further documents are listed in the continuation of Box C. <input type="checkbox"/> See patent family annex.		
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